Appendix D
NYSDOH guidelines for chemicals in air – development overview

As discussed in Section 3.2.5, the NYSDOH has developed several guidelines for chemicals in air. An overview of how the NYSDOH develops guidelines is provided in this appendix.

In general, the development of air guidelines can be divided into two parts: **toxicity assessment** and **exposure assessment**. In toxicity assessment, the scientific data on the toxicity and pharmacokinetics (i.e., the processes of absorption, distribution, metabolism and excretion) of a contaminant are evaluated to understand a chemical's potential for causing a health effect. In exposure assessment, scientific data are evaluated to determine the amount of air an individual breathes on a daily basis and how frequently and how long an individual may be exposed to a contaminant in air. Criteria based on cancer effects are generally expressed as the air concentration associated with a specific, excess lifetime cancer risk. Criteria based on non-cancer effects are generally expressed as a reference concentration, which is an air concentration that is expected to be without an appreciable risk of non-cancer health effects. These quantitative criteria are not, in themselves, standards. They are based solely on data and scientific judgments on the relationship between the level of contaminant in air and health risks, and do not reflect consideration of other factors, such as whether the concentration can be measured or whether the concentration is above background.

The first two steps of the toxicity assessment are

(1) Hazard Identification: What are the known or potential human health effects of an air contaminant? and
(2) Dose-Response Assessment: What is the potency (strength) of the contaminant to cause each type of known or potential human health effect?

All the relevant data are evaluated and summarized and a weight-of-evidence analysis is used to make these determinations. These determinations are then used to estimate numerical criteria (cancer risks and reference concentrations).

These estimations are carried out under the premises that

a. studies on effects in animals can be used to estimate the likelihood of effects in humans and
b. studies of effects of high exposure levels in humans or animals can be used to estimate the effects of low exposure levels.

Uncertainties present in these estimations include the following:

a. whether or not animals are good surrogates for humans,
b. whether or not the dose-response data provide reliable data on the critical effect and its lowest dose,
c. whether or not all critical effects have been identified (no data gaps), and
d. whether or not the methods used to extrapolate from the animals to humans and from high to low doses provide plausible estimates of risk at low doses.

In an exposure assessment for air, information is used that describes how much contaminated air a person may breathe each day. Estimations are also made about how frequently and how long people are exposed. The NYSDOH air guidelines are based on the assumption that people are continuously exposed to a contaminant in air all day, every day for as long as a lifetime.

The degree of confidence in the hazard identification and dose-response assessment is then summarized as part of the risk characterization (the last step in the risk assessment process), which describes the nature, strength of evidence, and the likelihood of adverse health effects from particular exposures.

The following two documents are included in this appendix to illustrate the development of a guideline:

- **TCE air guideline:** NYSDOH letter from N. Kim to D. Desnoyers, Division of Environmental Remediation, NYSDEC (October 31, 2003)

- **PCE air guideline:** Tetrachloroethene Health Effects. November 6, 1991. Appendix 1 of the Tetrachloroethene Ambient Air Criteria Document. Final Report. October 1997. Albany, NY: Bureau of Toxic Substance Assessment, Center for Environmental Health, New York State Department of Health.

For additional information on NYSDOH guidelines and criteria for these and other volatile chemicals in air (Section 3), please contact the NYSDOH's Bureau of Toxic Substance Assessment by calling 1-800-458-1158, or by emailing BTSA@health.state.ny.us, or by writing to the following address:

New York State Department of Health
Bureau of Toxic Substance Assessment
Flanigan Square, 547 River Street
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STATE OF NEW YORK
DEPARTMENT OF HEALTH

Flanigan Square, 547 River Street, Troy, New York 12180-2216

Antonia C. Novello, M.D., M.P.H., Dr.P.H.
Commissioner

Dennis P. Whalen
Executive Deputy Commissioner

October 31, 2003

Dale Desnoyers, Director
Division of Environmental Remediation
NYS Department of Environmental Conservation
625 Broadway
Albany, NY 12233-1080

Dear Mr. Desnoyers:

The New York State Department of Health has derived an air guideline for trichloroethene. Trichloroethene (TCE or trichloroethylene; CAS number 79-01-6) is a chemical commonly found in the environment, including the air (outdoor and indoor) that people breathe. This letter summarizes the important toxicological and epidemiological data we used to evaluate the potential health risks associated with exposure to TCE in air. We have followed the procedures outlined by the National Academy of Sciences and federal agencies such as the United States Environmental Protection Agency (US EPA), the United States Food and Drug Administration and the Agency for Toxic Substances and Disease Registry. These procedures are most recently described in US EPA documents (1994, 2000, 2002, 2003).

Human Non-Cancer Risks Associated with Exposure to TCE in Air

For non-cancer effects, points-of-departure (no-observed-effects levels or NOELs, lowest-observed-effects levels or LOELs, benchmark doses) were identified for target organs in humans and animals. Uncertainty factors were applied to the points-of-departure to estimate criteria for long-term exposure of the general population, including subpopulations that may be more vulnerable to TCE than other groups.

Typically, several uncertainty factors (generally, each is 3 or 10) are used to derive an exposure criterion from a point-of-departure. These uncertainty factors are intended to account for:

- the variation in sensitivity among the members of the human population;
- the uncertainty in extrapolating animal data to humans;
- the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure;
- the uncertainty in extrapolating from a LOEL rather than from a NOEL; and
- the uncertainty associated with extrapolation of results from adult humans or animals to children.

In humans, the central nervous system appears to be a sensitive indicator of TCE exposure, and there is concern that pre-natal TCE exposure may affect fetal development. In animals, TCE damages the central nervous system, liver, and kidneys of adult animals, and disrupts normal fetal development when exposure occurs during gestation. The animal data also suggest that the kidney effects generally occur at higher exposure levels than the other effects noted above.

Central Nervous System

Information on the central nervous system effects of TCE comes from studies of occupationally exposed workers and from studies of animals under controlled experimental conditions. In some occupational studies (Okawa and Bodner, 1973; Rasmussen et al., 1993; Vandervort and Polakoff, 1973), exposure to TCE is associated with effects on the central nervous system, including dizziness, headache, drowsiness, nausea and motor dyscoordination. Confidence in these studies for evaluating dose-response relationships is low because the studies did not provide adequate information on long-term TCE exposure and because the small numbers of workers who were examined were also exposed to chemicals other than TCE. Consequently, these data were not used to derive a potential criterion.

When adult male rats were exposed to TCE at 50 parts per million (ppm or 270 milligrams per cubic meter, mg/m^3) or more for eight hours per day, five days per week for six weeks, there were electroencephalographic (EEG) changes indicative of decreased wakefulness (Arito et al., 1994). The lowest exposure level in the study was an effect level. This level becomes 64 mg/m^3 after adjustment of the experimental exposure level to an equivalent level under conditions of continuous exposure (270 mg/m^3 x 8 hours/24 hours x 5 days/7 days = 64 mg/m^3). Using methods consistent with those recommended in the US EPA (1994) guidelines for deriving air criteria[1], the human adult equivalent concentration (HEC) is 64 mg/m^3. Adjusting the adult HEC to a child's HEC using a child's inhalation rate and body weight and applying an uncertainty factor of 3,000 to the child HEC suggests a potential criterion of about 9 microgram per cubic meter (9 mcg/m^3). The uncertainty factor was selected to compensate for use of a LOEL for an effect from a subchronic study in rats, human variability, and the potential increased sensitivity of children to TCE. Alternatively, applying a larger uncertainty factor to compensate for the observed effect (and an overall uncertainty factor of 10,000) suggests a potential criterion of 3 mcg/m^3.

Liver

Trichloroethene is also toxic to the liver of laboratory animals. Increases in absolute and relative liver weights were observed in male and female mice exposed continuously to 37 ppm (200 mg/m^3) or more for 30 days (Kjellstrand et al., 1983). We modeled the dose-response data for absolute liver weights and identified 13 ppm (70 mg/m^3) as the lowest air concentration corresponding to the lower bound on a 10% increase in liver effects in either male or female mice (essentially equivalent to a LOEL). Using methods consistent with those recommended in the US EPA (1994) guideline for deriving air criteria, the adult HEC is 70 mg/m^3. Adjusting the adult HEC to a child's HEC using a child's inhalation rate and body weight and applying an uncertainty factor of 3,000 to the child HEC suggests a potential criterion of about 9 mcg/m^3. The uncertainty factor was selected to compensate for use of a LOEL from a subchronic study in mice, human variability, and the potential increased sensitivity of children to TCE.

Developmental/Reproductive Effects

An epidemiological investigation (Goldberg et al., 1990) found an association between mothers living in areas where public drinking water wells were contaminated (primarily with TCE) and an increased incidence of cardiac malformations in their children. Whether or not prenatal TCE exposure played a role in producing these cardiac effects is unclear; however, this study raises concerns that developmental effects may be an important toxicological endpoint for TCE in humans.

In animals, Dawson et al. (1990, 1993) showed that exposure to TCE in drinking water during pregnancy caused a statistically significant increase in cardiac malformations in fetal rats at doses as low as 0.2 mg/kg/day. Applying an uncertainty factor of 1,000 to the animal LOEL and assuming

[1] For extrarespiratory effects of Type 3 chemicals such as TCE, the HEC equals the animal exposure concentration x an adjustment factor, which typically is a default value of 1 (US EPA, 1994).

that the inhaled and ingested doses of TCE (as mg/kg/day) are equivalent suggests a potential criterion of about 0.7 mcg/m^3. The uncertainty factor was selected to compensate for use of a LOEL in rats and human variability in the general population. Confidence in this potential criterion is lower than for those based on other animal studies.

Human Cancer Risks Associated with Exposure to TCE in Air

TCE is an animal carcinogen via the oral and inhalation routes of exposure, and evidence from occupational studies and drinking-water studies suggests that TCE is a risk factor for several types of cancer, including kidney, liver, and cancers of the lympho-hematopoietic systems (e.g., Non-Hodgkin's lymphoma (NHL) and Hodgkin's disease) (ATSDR, 1997; US EPA, 2001; Wartenberg et al., 2000). The National Toxicology Program has classified TCE as "*reasonably anticipated to be a human carcinogen.*" Similarly, the International Agency for Research on Cancer classifies TCE "*as probably carcinogenic to humans.*" In both cases, the determination was based on "limited evidence" of carcinogenicity from studies in humans and "sufficient evidence" of carcinogenicity from studies in experimental animals. In short, epidemiological studies suggest, but do not conclusively prove, that TCE increases the incidence of some types of cancer in humans, animal bioassay studies show unequivocally that oral or inhaled doses of TCE cause cancer at several sites in rats and mice, and mode-of-action data suggest that the way TCE causes cancer in animals may be relevant to humans.

For cancer effects, we identified the important human and animal studies on the carcinogenicity of TCE in air, and determined the appropriateness of each study for use in estimating the human TCE air concentration associated with an excess lifetime human cancer risk of one-in-one million. In both the qualitative and quantitative evaluation, we used procedures and methods consistent with the US EPA guidelines for carcinogen risk assessment (US EPA, 2003).

We evaluated four epidemiological studies to determine their usefulness to estimate the TCE air level (mcg/m^3) associated with an excess lifetime human cancer risk of 1×10^{-6} (i.e., a TCE 1×10^{-6} air level). Three of the studies (Anttila et al., 1995; Cohn et al., 1994; Henschler et al., 1995) did not meet minimal requirements (see Hertz-Picciotto, 1995) for use in dose-response assessment, largely because each study did not characterize adequately the duration and/or magnitude of exposure to TCE. The fourth study (Hansen et al., 2001) provided estimates of TCE air levels in the workplace and of the average duration of occupational exposures and was used to derive estimates of TCE 1×10^{-6} air levels.

Using the relative risk data (from Hansen et al., 2001), exposure data from occupational studies (Hansen et al., 2001; Raaschou-Nielsen et al., 2002) and an average relative risk model recommended by the World Health Organization (WHO, 1996), our estimates of the TCE 1 x 10^{-6} air levels range from about 0.06 to about 1 mcg/m^3 under a standard exposure scenario (continuous exposure for 70 years, 70-kg person, and inhalation rate of 20 m^3/day), and vary with choice of cancer site, measure of relative risk, the TCE workplace air level, and years of employment. Confidence in these estimates is low because of the small number of cases, the inability to adequately control the potential influence of confounders, unavoidable uncertainties in the exposure estimates, and the lack of clear dose-response relationship. Thus, these estimates were used to check the plausibility of animal-based estimates of 1 x 10^{-6} TCE air level (see below).

Inhalation studies using laboratory animals provide scientifically-sound, dose-response datasets showing a statistically significant relationship between TCE exposure levels and an increased incidence of tumors (Fukuda et al., 1983; Henschler et al., 1980; Maltoni et al., 1986). These data have been used by the US EPA (1987, 2001), CA EPA (1999, 2002), WHO (1996), Health Canada (1993), and Rhomberg (2000) to derive estimates of the TCE 1 x 10^{-6} air level.

We evaluated published estimates and derived additional estimates based on considerations of the quality of the animal data and the use of recommended dose metrics and cross-species extrapolation factors. The estimates considered in our evaluation were based on dose-response data from rats and mice for four cancer sites (liver, lung, testes, and lymph system) using three dose metrics (lifetime average daily exposure as TCE mg/m^3; lifetime average daily metabolized TCE dose as mg TCE metabolized/kg/day; or lifetime average daily internal dose of trichloroacetic acid (TCA) in plasma or tissue as TCA-area-under-curve (mg-hr)/liter), and two cross-species scaling methods (equal risk at equal exposure or equal risk at exposure scaled by body weight$^{0.75}$). The range of estimates of the TCE 1 x 10^{-6} air level is about 0.2 to about 4 mcg/m^3 under a standard exposure scenario (continuous exposure for 70 years, 70-kg person, and inhalation rate of 20 m^3/day). Because there is a lack of scientific consensus on the appropriate animal surrogate and cancer sites, dose metric, and the method for scaling dose across species, no single estimate is preferred. These estimates are similar to the estimates obtained from the human data.

Summary

We have evaluated the non-cancer effects associated with TCE exposure in air, and focused our attention on those studies that identified sensitive human and animal responses to TCE exposures. Three types of effects observed in animals were used: central nervous system (Arito et al., 1994), liver (Kjellstrand et al., 1983), and developmental (Dawson et al., 1990, 1993). Using methods consistent with latest US EPA guidelines, the potential criteria range from about 1 mcg/m^3 to about 10 mcg/m^3.

In developing these potential criteria, uncertainties that limit our ability to estimate the human non-cancer effects of low-dose exposures (i.e., use of subchronic studies to evaluate chronic exposures, use of an effect level rather than a no-observed-effect level, interspecies extrapolations, and human variability) and factors necessary when considering children (respiration rate and body weight of children and the potential increased sensitivity of children to TCE exposures) were taken into account.

We have evaluated the cancer effects associated with TCE exposure in air, and focused our attention on those human and animal studies that showed significant relationships between estimated or measured TCE exposure and increased rates of cancers. We did not find any human studies strong enough to support potential criteria (i.e., TCE 1 x 10^{-6} air levels) based on cancer effects, although one study (Hansen et al., 2001) was used for checking the plausibility of criteria based on animal studies.

We derived estimates of the TCE air level associated with an excess lifetime human cancer risk of 1 x 10^{-6} using data from inhalation studies using animals (Fukuda et al., 1983; Henschler et al., 1980; Maltoni et al., 1986). Given the lack of consensus on the appropriate data, we developed estimates based on two different species, four cancer sites, three different methods of estimating dose, and two different methods for scaling dose across species. Using methods consistent with latest US EPA guidelines, the potential criteria range from about 0.2 to about 4 mcg/m^3. This range reflects the uncertainty surrounding our ability to estimate the human cancer effects of low-dose exposures. The animal-based estimates are similar to the human-based estimates.

After reviewing the data on the non-cancer and cancer effects of TCE and the potential criteria for long-term exposure of the general populations based on these effects, the New York State Department of Health has set an air guideline for TCE of 5 mcg/m^3. The margins-of-exposure between this guideline and the TCE air levels known to cause non-cancer effects in animals are consistent with recommended procedures and are adequate when

considered in conjunction with the limitations of the different studies. Similarly, the estimated increased human cancer risks associated with lifetime continuous exposure to 5 mcg/m^3 are in the risk range (1×10^{-6} to 1×10^{-4}) that is generally used by regulatory agencies when making decisions. We continue to update, review, and refine our evaluation of the potential health risks associated with TCE.

Sincerely,

Nancy K. Kim

Nancy K. Kim, Ph.D., Director
Division of Environmental Health Assessment

Enclosure
cc: R. Tramontano
C. Johnson

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FINAL REPORT

TETRACHLOROETHENE AMBIENT AIR CRITERIA DOCUMENT

OCTOBER 1997

New York State
Department of Health

CENTER FOR ENVIRONMENTAL HEALTH
BUREAU OF TOXIC SUBSTANCE ASSESSMENT

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Albany, NY 12203-3399

APPENDIX 1

TETRACHLOROETHENE
HEALTH EFFECTS

November 6, 1991

NEW YORK STATE DEPARTMENT OF HEALTH

TETRACHLOROETHENE HEALTH EFFECTS

November 6, 1991

In evaluating the health risks from tetrachloroethene exposure, the New York State Department of Health followed the procedures outlined by the National Academy of Sciences (NAS, 1977, 1987) and federal agencies such as the U.S. Food and Drug Administration, the U.S. Environmental Protection Agency, and the Agency for Toxic Substances and Disease Registry (Dourson and Stara, 1983; US EPA 1988, 1989). We've identified either no-observed-effect levels or lowest-observed-effect levels for target organs in humans and animals. When developing exposure guidelines for long-term exposure of the general population from human data, uncertainty factors are used because effect or no-effect levels can be based on studies using healthy adults (frequently only men), short exposure times, small sample sizes and limited information on exposure levels. These same limitations may exist when using animal data, but additional uncertainty is introduced when extrapolating results from animals to humans. Uncertainty factors that are usually applied include a factor of ten for a short-term study, ten for using a lowest-observed-effect level rather than a no-observed-effect level and ten in going from a limited study in adults to the general population. Consideration may also be made for the quality and quantity of the available data.

Information on central nervous system effects comes from human controlled-chamber exposures and from epidemiological studies. The controlled studies used healthy adults and short exposure times. The epidemiological studies involved longer exposure times, but the exposure levels are less certain than for the controlled studies.

In controlled exposure studies, Stewart et al. (1970) and Hake and Stewart (1977) reported central nervous system effects when adult males and females were exposed to 100 ppm (690 milligrams per cubic meter--mg/m^3) for 7 or 7.5 hours per day for five days. Effects were not detected in adults exposed to 20 ppm (140 mg/m^3) for 7.5 hours per day for 5 days.

Workers exposed to tetrachloroethene have also been evaluated for possible central nervous system effects. A study by Lauwerys et al. (1983) did not detect adverse effects on the central nervous system of Belgian workers at dry cleaning shops who were exposed to a time weighted average (TWA) tetrachloroethene level of 21 ppm (145 mg/m^3). Seeber (1989) summarized a series of studies which evaluated such endpoints as perceptual speed, digit reproduction and sensorimotor and coordination functions in German dry cleaning workers. The performance of both the high-exposed (reported TWA 360 mg/m^3) and low-exposed (reported TWA 83 mg/m^3) groups differed significantly from the control group for some tests; however, the two exposed groups did not differ from each other.

A guideline for central nervous system effects for the general population can be derived from the no-observed-effect level in controlled chamber experiments or from the worker studies. The no-observed-effect level for central nervous system effects in the controlled chamber studies is 20 ppm (140 mg/m^3). Because this study was on healthy adults and of limited duration, an uncertainty factor of 100 is applied after averaging the concentration over 24 hours. This suggests a guideline of 0.4 mg/m^3. The lowest effect level in the worker studies was 83 mg/m^3. Because effects were observed and the study was on healthy adults, an uncertainty factor of 100 is needed after averaging the concentration over 24 hours. This suggests a guideline of 0.25 mg/m^3.

The liver is also a target organ for tetrachloroethene, particularly in mice. Case reports of liver effects have also been reported in humans who were exposed to high concentrations, sometimes under severe circumstances. The lowest-observed-effect level for mice is 60 mg/m³, when continuously exposed for 30 days (Kjellstrand et al., 1984). Liver weights were significantly elevated. Using an inhaled dose to extrapolate the results from mice to humans and applying a thousand-fold uncertainty factor would suggest a guideline of about 0.25 mg/m³ for liver effects.

The kidney is also a target organ in rats. Effects were seen in rats exposed to 200 ppm (1,400 mg/m³) for 6 hours per day, 5 days per week for 2 years (NTP, 1986). These effects included nucleus enlargement and tubular cell hyperplasia. Using an inhaled dose to extrapolate from rats to humans and applying a thousand-fold uncertainty factor would suggest a guideline of about 0.5 mg/m³ for kidney effects.

Exposure to tetrachloroethene caused liver tumors in mice and mononuclear cell leukemias and kidney tumors in rats. The exact mechanisms by which these tumors were induced are not known. Because of the uncertainty, a conservative estimate of the tetrachloroethene air concentration corresponding to the upper bound on risk and associated with a one in one million excess lifetime human oncogenic risk is 0.00005 mg/m³. This estimate is based on the assumptions that the delivered dose of the active carcinogenic agent is linearly proportional to the inhaled dose of tetrachloroethene across all doses and that surface area is the appropriate parameter for dose extrapolation. Confidence in this estimate is limited by the data which indicate that linearity across all doses does not hold for the potential oncogenic agents (tetrachloroethene or its metabolites) and by the degree to which the results of empirical observations on the toxic effects of anti-neoplastic drugs (the source of the surface area rule) are applicable to chemicals which are metabolized differently.

Correlations between the metabolic and carcinogenic data can be used to support the hypothesis that the metabolic products of the mixed function oxidase pathway for tetrachloroethene are responsible for its carcinogenicity in mice. If the available data are used with physiologically-based pharmacokinetic modeling, an estimate of the air level corresponding to the upper bound on risk and associated with a one in one million excess lifetime human carcinogenic risk is 0.0005 mg/m³ (if humans and mice are assumed to be equally sensitive to the same delivered dose). Confidence in this estimate is limited by the validity of the initial assumptions and the accuracy of the model in compensating for non-linearity when extrapolating from high to low doses and in compensating for differences in the capacity of mice and humans to metabolize tetrachloroethene by the mixed function oxidase pathway.

Correlations using urinary excretion data for tetrachloroethene metabolites can also be used to estimate an excess human cancer risk from the mouse liver tumor data. Using this method (US EPA, 1990), the tetrachloroethene air concentration corresponding to an upper bound on risk and associated with a one in one million excess lifetime human cancer risk is 0.002 mg/m³.

The New York State Department of Health recommends, based on an evaluation of the non-carcinogenic effects of tetrachloroethene, that the average ambient air level in a residential community not exceed 0.25 mg/m³ for adults, considering continuous lifetime exposure. If a child's inhalation rate and body weight are used, the guideline becomes 0.1 mg/m³. Furthermore, we recommend that the uncertainty factor not be reduced by more than an order of magnitude when considering the need to take immediate action. We also recommend that exposure to tetrachloroethene be minimized to the extent practical; e.g. regardless of the levels, solvent containers should not be left opened. The potential carcinogenic risks of tetrachloroethene will be considered further as regulations are developed for the dry cleaning industry.

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EXPOSURE ASSUMPTIONS USED TO DERIVE 1991 GUIDELINES

The exposure assumptions used to derive the non-carcinogenic guidelines are provided below.

Group	Body Weight	Daily Inhalation Rate
adult	70 kg	20 m^3/day
child	20.5 kg*	14.5 m^3/day*
mouse	0.035 kg	0.039 m^3/day
rat	0.40 kg	0.24 m^3/day

*see Table 12 of Criteria Document for age-specific data

The methods and assumptions used to derive the carcinogenic guidelines based on metabolized dose are found in Table 17 of Criteria Document.

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